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Functional computed tomography in oncology

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Abstract

Functional Computed Tomography (CT) describes the use of existing technologies and conventional contrast agents to capture physiological parameters that reflect the vasculature within tumours and other tissues. The technique is readily incorporated into routine conventional CT examinations and, in tumours, the physiological parameters obtained provide an *in-vivo* marker of angiogenesis. As well as providing a research tool, functional CT has clinical applications in tumour diagnosis, staging, risk stratification and therapy monitoring, including the characterisation of pulmonary nodules, detection of occult hepatic metastases, grading of cerebral glioma and monitoring of anti-angiogenesis drugs. With the recent commercial availability of appropriate software and the development of multislice CT systems, functional CT is poised to make a significant impact upon the imaging of patients with cancer.

Keywords: Functional Computed Tomography; Angiogenesis; Perfusion; Review; Imaging

1. Introduction

Functional computed tomography (CT) describes the use of existing technologies and conventional contrast agents to capture physiological parameters that reflect the vasculature within tumours and other tissues. This is achieved by measuring the temporal changes in contrast enhancement from a series of CT images acquired over time. Some functional CT techniques use simple measures of tissue contrast enhancement such as peak enhancement value or maximal enhancement rate, to obtain semi-quantitative assessments of vascular physiology. However, by considering contrast agents as physiological indicators and with appropriate physiological modelling, it is also possible to determine absolute values for tissue perfusion, relative blood volume, capillary permeability and leakage (extracellular) space. These parameters provide physiological correlates for the microscopic changes that occur with tumour angiogenesis [1,2].

Tumour angiogenesis is characterised morphologically by increased numbers of small blood vessels. These microvessels are too small to image directly (<0.1 mm), but their increased density translates *in vivo* to increased tumour perfusion and blood volume. Tumour microvessels also have incomplete basement membranes that are abnormally leaky to circulating molecules, including contrast agents, resulting in increased permeability and leakage space measurements on functional CT. In general, permeability measurements are most applicable to the brain where permeability levels within tumours are considerably higher in comparison to the almost impermeable blood-brain barrier. Within other body regions, the differences in permeability between malignant and normal tissues are lower and measurements of tumour perfusion and blood volume are more appropriate. More recently, the Standardised Perfusion Value (SPV), a parameter that corrects perfusion values for patient weight and cardiac output, has been suggested as a more appropriate measure for assessing angiogenesis [3]. The SPV has a similar mathematical derivation to the Standardised Uptake Value (SUV) used to quantify tumour uptake of fluorodeoxyglucose during Positron Emission Tomography (PET) and a correlation between the CT derived SPV and PET measurements of SUV has been shown for lung masses [3].

When first introduced by Godfrey Hounsfield in 1971, CT was immediately recognised as a major advance on account of its ability to demonstrate internal anatomy.

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The ability of CT to quantify physiological processes was first shown by Axel 8 years later [4], but the speed of image acquisition and data processing at that time was too slow for the technique to become widely accepted. During the 1980s, use of functional CT was largely confined to studies of myocardial and renal blood flow using electron beam CT systems, restricting its application to research [5,6]. The application of the techniques to conventional CT systems was promoted by the development of faster spiral CT systems in the 1990s [7]. The first report of CT measurements of tumour perfusion using a spiral CT system was a study of hepatic perfusion, including patients with metastases in 1993 [8].

1.1. Physiological models

Two alternative modelling approaches are available for derivation of physiological parameters from temporal changes in contrast enhancement on CT: compartmental analysis and deconvolution [2]. Both methods require time-attenuation data from the arterial system (input function) to correct for interpatient variations in bolus geometry.

Compartmental analysis uses a single-compartment model based on the Fick principle to estimate tumour perfusion. Perfusion is calculated from the maximal slope of the tissue concentration–time curve or from its peak height, normalised to the arterial input function [2]. Normalising perfusion measurements to mean whole body perfusion as determined from the ratio of cardiac output to body weight, gives the Standardised Perfusion Value (analogous to the Standardised Uptake Value widely used in fluorine-labelled deoxyglucose (FDG)-PET in which tissue FDG uptake is normalised to average whole body uptake) [3]. A two-compartment model is used to determine capillary permeability and blood volume [2].

Deconvolution is a mathematical technique that uses the arterial and tissue concentration-time curves to calculate the Impulse Residue Function (IRF) for the tissue of interest, where the IRF is a theoretical tissue curve that would be obtained from an instantaneous arterial input. The IRF is usually constrained in its shape to comprise a plateau followed by a single exponential decay. The height of the flow corrected IRF will give the tissue perfusion and the area under the curve will determine the relative blood volume. This approach can also be extended to include a measurement of capillary permeability by use of a distributed parameter model [2].

1.2. The need for in vivo markers of angiogenesis

The development of a tumour blood supply through the processes of angiogenesis is essential for the growth of tumours. Prior to this angiogenesis phase, the size of early tumours is restricted to 2–3 mm by the lack of access to circulating oxygen, nutrients and growth factors. The ability of tumours to metastasise is also believed to be angiogenesis-dependent and highly vascularised tumours have been shown to be associated with a poor outcome for many types of cancer [9,10] Thus an *in vivo* marker of angiogenesis, obtained through non-invasive imaging, could provide an independent indicator of prognosis, enabling risk stratification for patients with cancer.

An effective imaging strategy for assessing tumour angiogenesis would also be of value to monitor 'anti-angiogenesis' drugs. 'Anti-angiogenesis' is an emerging strategy for cancer therapy in which the aim is to halt cancer progression by suppressing the tumour blood supply. On the basis of supportive animal studies and case reports, more than three dozen anti-angiogenesis drugs are currently in human clinical trials. It has been estimated that $4 billion has been invested worldwide to develop such agents, making this one of the most heavily invested areas of cancer research in human history [11]. A broad range of therapeutic targets have emerged including antagonists to growth factors such as Vascular Endothelial Growth Factor (VEGF), inhibition of endothelial cell signal transduction or proliferation, inhibition of matrix metalloproteinases, endothelial surface marker targeting and endothelial cell destruction [11].

Early clinical trials have indicated that conventional imaging strategies are not suitable for monitoring the effects of anti-angiogenesis drugs [11]. Most of these agents are not directly cytotoxic to tumour cells and produce disease stabilisation rather than tumour regression [11]. Thus, evaluation of tumour size alone is ineffective. Non-imaging approaches, such as measurement of growth factors in serum or urine, are yet to be fully validated and serial tumour biopsies with determination of microvessel density (MVD) is invasive, prone to sampling error and impractical for the large numbers of patients required in late-stage clinical trials. Existing functional imaging techniques, such as FDG-PET, that are not directed at the vascular system may also be inappropriate due to anti-angiogenesis drug-induced uncoupling of tumour perfusion and other aspects of tumour physiology [12]. Thus, novel imaging strategies that are capable of depicting tumour vascularity in a sensitive and specific manner are required to enable monitoring of tumour angiogenesis *in vivo*.

CT has continued to provide the mainstay for anatomical imaging in oncology and functional CT can be readily incorporated into existing CT protocols, adding only a few minutes to the procedure. Thus, functional CT is well suited for the *in-vivo* assessment of angiogenesis for patients with cancer, avoiding the need for an additional imaging modality. Perfusion CT produces

reproducible measurements [13] that have been validated against a number of reference methods including O^{15}-water PET and microspheres [14–18]. The additional radiation exposure is approximately 1 to 5 mSv, depending on the body region examined. (Annual background radiation exposure is approximately 2 mSv.) Commercially available software packages are now available for calculating functional CT parameters with the generation of colour-coded parametric maps (Fig. 1). The linear relationship between contrast medium concentration and CT attenuation value means that quantification is much simpler with CT than for magnetic resonance (MR) [2].

2. Current status of functional CT in oncology

To date, clinical experience with functional CT has for the most part comprised of preliminary series with a few large-scale clinical trials. However, these reports have demonstrated a range of promising applications for functional CT within each of the main areas for which imaging is used in oncology, specifically diagnosis, staging, assessment of tumour grade and prognosis, and therapy monitoring.

2.1. Diagnosis

It is often difficult to distinguish benign from malignant lesions using conventional structural imaging criteria, for example, in the relatively common diagnostic problem of the solitary pulmonary nodule (SPN). In a series of 107 patients, Swensen and colleagues [19] were able to distinguish benign from malignant nodules using simple measurements of peak enhancement on CT. Peak enhancement, a semi-quantitative measure of perfusion [1], was also shown to correlate with histological assessments of microvessel density. A subsequent multicentre trial of 356 patients demonstrated a sensitivity of 98% and specificity 58% [20] for SPN enhancement values in the diagnosis of malignancy within nodules that were otherwise indeterminate on conventional CT. Zhang and Kono [21] have shown similar results for other functional CT parameters, including dedicated perfusion measurements. As mentioned above, CT perfusion measurements have been shown to correlate with PET measurements of FDG uptake within SPNs [3], probably reflecting that angiogenesis and increased glucose metabolism are different phenotypic manifestations of a common oncogene mutation (e.g. the *P53* oncogene). FDG-PET is also emerging as an effective imaging modality for the characterisation of SPNs, particularly when CT is indeterminate. By reducing the number of indeterminate CT results, the high negative predictive value of functional CT as an adjunct to a conventional CT examination may lessen the numbers of patients requiring PET, thereby saving on health care expenditure. Furthermore, combining measurements of FDG uptake in SPNs with functional CT measurements of nodule perfusion FDG, has the potential to reduce the number of false-positive PET results. This combined approach may be especially applicable to the recently developed integrated CT/PET systems.

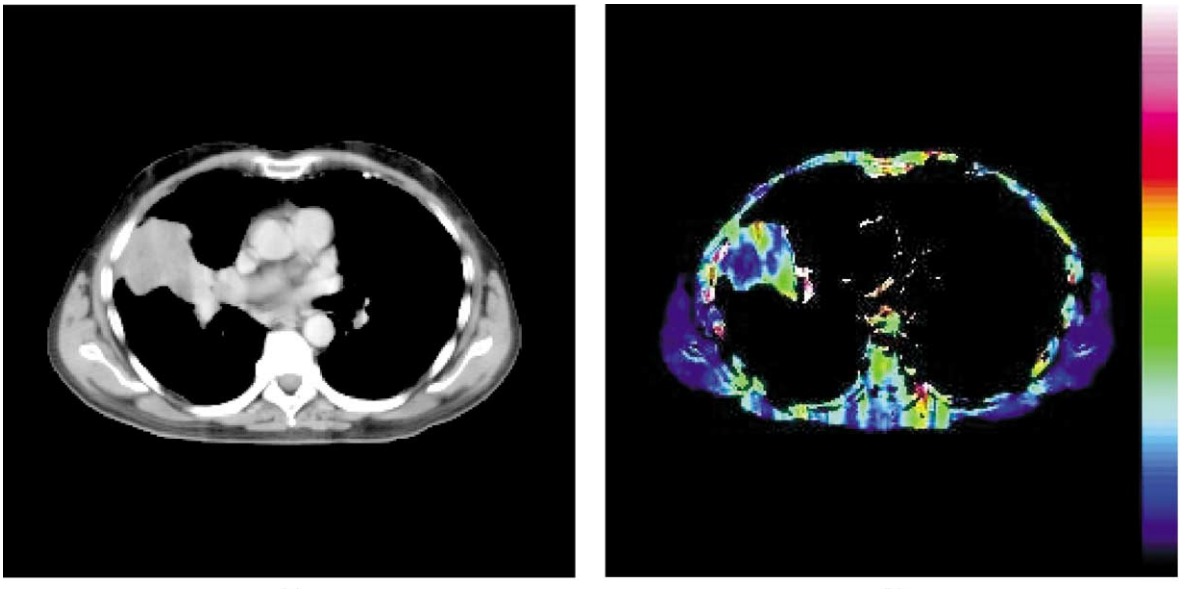

Fig. 1. Contrast enhanced Computed Tomography (CT) (a) and perfusion CT (b) from a patient with a right-sided lung cancer. The degree of contrast enhancement and perfusion is determined by angiogenesis, enabling distinction between benign and malignant lung lesions and providing prognostic information.

2.2. Staging

Despite advances in liver imaging, occult hepatic metastases continue to present a significant diagnostic problem. Many patients with an apparently normal liver at initial staging subsequently develop overt metastases, probably due to the presence of lesions too small to be detected at the initial examination. Angiogenesis develops in metastases when only 200 μm in diameter and thus even small tumours are associated with alterations in liver blood flow that could allow detection of metastases prior to visualisation as discrete masses on structural conventional imaging (typically 3 mm minimum). Using functional CT, these haemodynamic changes have been shown to be detectible in experimentally induced metastases with a mean size of 500 μm [22]. Such flow changes can also be appreciated as increased hepatic parenchymal enhancement during dual-phase spiral CT with increased arterial phase enhancement heralding the subsequent development of overt lesions [23,24]. Occult hepatic metastases have also been identified as areas of high perfusion on CT derived images of hepatic perfusion [25,26]

Nodal staging with conventional CT, which relies on size criteria alone, fails to detect small tumour-bearing nodes and may falsely diagnose enlarged reactive nodes as malignant. However, the determination of nodal status in gastric cancer can be improved by quantifying contrast enhancement within nodes [27]; malignant nodes enhance more avidly reflecting tumour-associated angiogenesis. The potential for such functional CT techniques to diagnose nodal metastases for other tumours remains to be determined.

2.3. Grading and prognosis

The ability to determine tumour grade *in vivo* by using imaging avoids the biopsy-sampling error that may occur with histological evaluations due to tumour heterogeneity. Imaging assessments are also of value when a biopsy is difficult or as an alternative to repeated biopsy when there is a propensity for the tumour grade to change with time. Due to the relative invasive nature of a cerebral biopsy, imaging has gained an important role in the assessment of grade for cerebral glioma in particular. Histological assessments of tumour angiogenesis in gliomas, such as VEGF and MVD, have been shown to correlate with tumour grade; high grade tumours demonstrate greatest vascularisation. Within low grade tumours, the same markers of angiogenesis correlate with a shorter survival time and a greater likelihood of malignant transformation [28]. Functional CT techniques that quantify cerebral blood volume and blood–brain barrier permeability provide an imaging correlate for these angiogenic changes. High-grade tumours demonstrate increased blood volume and heterogeneity on blood volume images [29]. There is also potential for CT measurements of blood–brain barrier permeability to provide an indication of tumour grade analogous to dynamic contrast enhanced MR techniques [30]. Experience with functional CT in grading other tumours is limited, but CT perfusion values above 0.5 ml/min/ml in lymphoma masses have been shown to imply high or intermediate grade tumour [31].

Risk stratification is an emerging aspect of cancer care with the potential to individualise the patient's treatment by matching the therapy to the tumour biology. Patients with aggressive tumours may be suitable for additional treatment or invasive local treatments could be withheld when unlikely to be of benefit. The ability for angiogenesis to provide a prognostic marker may be reflected *in vivo* by functional CT measurements. For example, CT perfusion values in lung cancer have been shown to be higher in tumours of more advanced stage [32] and also to correlate with measures of FDG uptake, another recognised prognostic marker [3]. CT measurements of perfusion in head and neck cancers have been shown to be significantly different between tumours with a favourable and those with an unfavourable outcome following radiotherapy [33].

Within the liver, the relationship between angiogenesis and hepatic perfusion is more complex. Hepatic metastases derive their blood supply almost exclusively from the arterial system whereas the portal circulation in surrounding liver can be affected by mechanical compression by enlarging metastases, by white cell margination within portal vessels adjacent to metastases and by circulating hormonal factors [26]. The physiological linkage between arterial and portal circulations such that reduced portal flow is associated with increased arterial flow, complicates the situation further. Histological studies have shown that, unlike primary tumours, greater vascularisation of hepatic metastases is associated with a better prognosis [34]. This association is reflected by perfusion CT findings amongst patients with hepatic metastases. Increased arterial perfusion, particularly in the periphery of the metastasis, is associated with a longer survival [35] (Fig. 2) whereas a small series of patients with hepatic metastases from colon cancer has suggested that low portal perfusion throughout the liver (i.e. below 0.22 ml/min/ml) is associated with progressive disease and a poor response to chemotherapy [25,36].

2.4. Therapy monitoring

For the reasons described above, functional CT is well placed to provide a means for monitoring the effects of anti-angiogenesis drugs, both in a research context and as a clinical procedure for individual patients. Although studies have shown that anti-angiogenesis therapies reduce tumour perfusion, to date this has not been

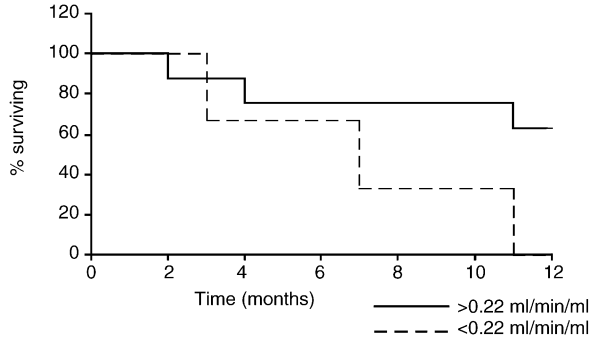

Fig. 2. Risk-stratification using functional Computed Tomography (CT). Survival is poorer amongst patients with metastases from colorectal cancer and reduced hepatic portal perfusion.

demonstrated using functional CT. However, there have been studies where drug-induced changes in vascular physiology have been measured using functional CT. Therefore, functional CT may also be useful as a general indicator of therapeutic response on the basis that angiogenesis, and its physiological imaging correlates, can be used as a marker of tumour activity. Changes in the permeability of cerebral glioma in response to steroid therapy and to the bradykinin analogue RMP-7 have been demonstrated using functional CT [37,38]. Functional CT has also shown reduced values of perfusion within lymphoma masses following successful chemotherapy and reductions in perfusion during treatment of metastatic colon cancer with BW12C [39].

3. Future directions

Until recently, the broader application of functional CT techniques has been hindered by the lack of commercially available software to perform the more precise quantitative analyses that calculate perfusion, blood volume and capillary permeability. Although simple densitometric analyses, such as peak enhancement values, are relatively straightforward to perform using standard CT software, they are likely to be less accurate as they do not correct for variations in the vascular input. However, the last few years have seen several CT manufacturers develop functional CT software packages, including dedicated algorithms for tumour imaging. With the recent commercial release of these packages leading to a wider availability of functional CT, more extensive clinical data can be anticipated.

With the advent of multislice CT systems, some technical developments in functional CT are likely. In particular, multislice CT will enable physiological parameters to be captured over larger tissue volumes that include the whole tumour, removing the current limitation of a single-slice study generally required for dedicated perfusion and permeability measurements. More sophisticated CT technologies that vary the X-ray exposure during the scan rotation may allow reductions in the radiation dose associated with repeated volume acquisitions. CT systems that offer respiratory gating as a means to reduce misregistration artefacts for abdominal functional CT are also under development. New image acquisition protocols will enable measurement of multiple physiological parameters in one examination. Development of new contrast agents with longer intravascular residence times may also overcome some of the complexities of physiological modelling required for conventional contrast agents that exhibit two-compartment pharmacokinetics.

Validation of functional CT parameters as markers of angiogenesis is currently under way at several institutions by comparing functional CT measurements with histological assessments of angiogenesis in various tumour types. A recent study of peak contrast enhancement in lung adenocarcinomas measured on CT has demonstrated a significant correlation with microvessel density and VEGF expression [40]. Similarly, peak enhancement in renal tumours correlates with MVD [41]. Although peak enhancement is a measure of perfusion, these studies could be usefully repeated with more specific CT-based physiological measurements. The direct validation of functional CT as an *in-vivo* marker of angiogenesis will establish the suitability of the technique for monitoring anti-angiogenesis drugs and promote more extensive clinical trials.

4. Summary

Although a detailed knowledge of the structure of the vascular system existed as early as the second century AD, it was 1500 years later that William Harvey demonstrated the circulatory nature of blood flow. Functional CT makes the same transition from structure to function for Computed Tomography capturing the physiological parameters that reflect the vasculature within tumours and so providing a means to assess tumour angiogenesis *in vivo*. Functional CT is readily incorporated into the patient's routine conventional CT examination and the additional information can assist with diagnosis, staging, risk stratification and therapy monitoring for patients with cancer.

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